

09/919,195

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FILE 'HOME' ENTERED AT 09:13:52 ON 18 MAR 2003

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=> d his

(FILE 'HOME' ENTERED AT 09:13:52 ON 18 MAR 2003)

FILE 'CA' ENTERED AT 09:13:58 ON 18 MAR 2003

L1 136887 S LUNG
L2 2349 S ALVEOLI
L3 1993 S ATRA
L4 4106 S ALL-TRANS-RETINOIC ACID
L5 4119 S ALL-TRANS-RETINOIC
L6 3335 S RAR
L7 243391 S MODULAT?
L8 431 S L6 AND L7
L9 295 S L8 AND PY<2000

=> s 19 and (l1 or l2 or l3 or l5)

L10 103 L9 AND (L1 OR L2 OR L3 OR L5)

=> d 103 ibib abs kwic

L10 ANSWER 103 OF 103 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 112:230122 CA

TITLE: Indirect effects of histamine on pulmonary rapidly adapting receptors in cats

AUTHOR(S): Yu, Jun; Roberts, Andrew M.

CORPORATE SOURCE: Sch. Med., Univ. Louisville, Louisville, KY, 40292, USA

SOURCE: Respiration Physiology (1990), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The relative importance of lung mech. changes during histamine-induced activation of pulmonary rapidly adapting receptors (RARs) was investigated. In anesthetized, open-chest, artificially ventilated cats, the authors recorded RAR activity and injected histamine (25-50 $\mu\text{g/kg}$) into the right atrium. Histamine initially increased RAR activity from 1.1 to 3.6 imp/s at 15.6 s when dynamic lung compliance (CDYN) was decreased by 29.1%. The firing pattern of RARs changed from a relatively irregular pattern to a pronounced respiratory modulation. RAR activity reached its peak (5.6 imp/s) at 36.3 s. The firing pattern further changed to a cardiac modulation, and the activity closely correlated with cardiac output. On comparing the initial response of RARs to histamine with the response to mech. decreasing CDYN, the activities were similar when CDYN was decreased by the same amt. In cats, the initial increase of RAR activity in response to histamine is apparently related to lung mech. changes, but the later increase is related to cardiovascular functions.

SO Respiration Physiology (1990), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687

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ST histamine **lung** rapidly adapting receptor; cardiovascular system
IT **lung** histamine; receptor **lung** compliance histamine
IT Blood pressure
(histamine effect on, **lung** rapidly adapting receptors in relation to)
IT **Lung**, composition
(rapidly adapting receptors of, histamine effect on)
IT 51-45-6, Histamine, biological studies
RL: BIOL (Biological study)
(**lung** rapidly adapting receptors response to)

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L1 136887 S LUNG
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L6 3335 S RAR
L7 243391 S MODULAT?
L8 431 S L6 AND L7
L9 295 S L8 AND PY<2000
L10 103 S L9 AND (L1 OR L2 OR L3 OR L5)

FILE 'STNGUIDE' ENTERED AT 09:16:29 ON 18 MAR 2003

FILE 'CA' ENTERED AT 09:16:43 ON 18 MAR 2003

=> d l10 100-102 kwic

L10 ANSWER 100 OF 103 CA COPYRIGHT 2003 ACS
SO Cell (Cambridge, MA, United States) (1992), 68(2), 397-406
CODEN: CELLB5; ISSN: 0092-8674
AB **all-trans Retinoic acid** (RA) has previously been shown to **modulate** the transcriptional properties of the retinoic acid receptor (**RAR**) and retinoid X receptors (**RXR**). The inability of **all-trans RA** to bind to **RXR** suggests that it may be metabolized. . .
IT Receptors
RL: BIOL (Biological study)

- (**RAR**-.alpha. (retinoic acid receptor .alpha.)), activation of,
by cis- and all-trans-retinoates, retinoate distribution in mammal in
relation to)
- IT Retinoids
RL: BIOL (Biological study)
(**RAR**-.alpha. receptors, activation of, by cis- and
all-trans-retinoates, retinoate distribution in mammal in relation to)
- IT Isomerization
(cis-trans, photochem., of retinoate, distribution in mammal and
activation of retinoate receptors RXR.alpha. and **RAR**.alpha.
in relation to)
- IT 302-79-4, **all-trans Retinoic acid**
RL: BIOL (Biological study)
(retinoic acid receptors RXR.alpha. and **RAR**.alpha. activation
by, cis-retinoate in relation to)
- L10 ANSWER 101 OF 103 CA COPYRIGHT 2003 ACS
- TI **All-trans retinoic acid modulates**
the retinoic acid receptor-.alpha. in promyelocytic cells
- SO Journal of Clinical Investigation (1991), 88(6), 2150-4
CODEN: JCINAO; ISSN: 0021-9738
- AB It was recently demonstrated that **all-trans**
retinoic acid (RA), the active metabolite of vitamin A, is an
efficient alternative to chemotherapy in the treatment of acute
promyelocytic leukemia (AML3). It was further shown that, in these AML3
cells, the gene of the retinoic acid receptor-.alpha. (**RAR**
.alpha.) is translocated from chromosome 17 to chromosome 15, and fused to
a new gene, PLM. This results in the expression of both normal and
chimeric **RAR**.alpha. transcripts in AML3 cells. The PLM-
RAR.alpha. protein may account for the impairment of
differentiation and thus leukemogenesis, but not for the paradoxical
efficacy of RA in. . . an attempt to elucidate RA's differentiative
effect in AML3 patients, the present work examd. the in vitro and in vivo
modulation of the normal **RAR**.alpha. transcripts by
all-trans RA in seven cases of AML3. In all samples, Northern blot anal.
revealed a low expression of the two normal **RAR**.alpha.
transcripts compared with other human myeloid leukemic cells. No
modulation was obsd. after 4-8 d of in vivo therapy with all-trans
RA 45 mg/m2 per d. In vitro incubation with all-trans RA, however,
increased the level of expression of the normal **RAR**.alpha.
transcripts in AML3 cells but not in other AML leukemic subtypes. This
modulation of the two normal **RAR**.alpha. transcripts
appeared to be an early and primary event of RA's differentiating effect.
Apparently, up-regulation of the normal **RAR**.alpha. gene
expression by pharmacol. concns. of all-trans RA may restore the normal
differentiation pathway in these cells.
- IT Receptors
RL: BIOL (Biological study)
(**RAR**-.alpha. (retinoic acid receptor .alpha.)), in
promyelocytic leukemia of humans inhibition by retinoic acid)
- IT Retinoids
RL: BIOL (Biological study)
(**RAR**-.alpha. receptors, in promyelocytic leukemia of humans
inhibition by retinoic acid)
- L10 ANSWER 102 OF 103 CA COPYRIGHT 2003 ACS
- TI **Modulation** by retinoids of mRNA levels for nuclear retinoic acid
receptors in murine melanoma cells
- SO Molecular Endocrinology (1990), 4(10), 1546-55
CODEN: MOENEN; ISSN: 0888-8809

09/919,195

AB' . . . S91-C2 melanoma cells. Specific alterations in gene expression are a plausible mechanism for these effects. Since nuclear retinoic acid receptors (RAR) are likely mediators of retinoid-induced changes in gene expression, Northern blotting was used to analyze the expression of RAR.alpha., RAR.beta., and RAR.gamma. in S91-C2 cells. mRNA for both RAR.alpha. and RAR.gamma. was detected in these cells, but no RAR.beta. mRNA could be found. Treatment with 10⁻⁷ and 10⁻⁶M .beta.-all-trans-retinoic acid (RA) for 24 h caused a 1.5-2-fold increase in RAR.alpha. and RAR.gamma. mRNA, whereas lower concns. of RA were ineffective. RAR.beta. mRNA, which was undetectable in untreated cells, was detected after 24 h of treatment with a RA concn. as low as 10⁻⁹M, and its level increased with up to 10⁻⁶M RA. At the latter dose, RAR.beta. mRNA induction occurred by 4 h and increased progressively, reaching a plateau after 24 h of treatment. RAR.beta. mRNA induction at 4 h was not inhibited by cycloheximide at a concn. that suppressed protein synthesis by more than. . . Several retinoids and related synthetic compds., including 13-cis RA, TTNPB, Ch55, Am80, and the trifluoromethylnonyloxyphenyl analog of RA, also induced RAR.beta. mRNA, whereas a 24-h treatment with 10⁻⁶M retinol, TTNP (a decarboxylated analog of TTNPB), or the Ph analog of RA failed to induce RAR.beta. mRNA. With the exception of retinol and the trifluoromethyl nonyloxyphenyl analog of RA, the ability of the retinoids to induce RAR.beta. mRNA and their growth inhibitory effect were correlated. However, S91-C154, a RA-resistant mutant subclone derived from S91-C2 cells, showed mRNA levels of RAR.alpha. and RAR.gamma. and induction of RAR.beta. by RA similar to those detected in the sensitive S91-C2 cells. Like the S91 melanoma cells, two other mouse melanoma cell lines, K-1735P and B16-F1, constitutively expressed RAR.alpha. and RAR.gamma. mRNAs. The level of RAR.beta. mRNA was increased by RA only in B16-F1 cells, although the growth of both was inhibited by RA. These results. . .

ST nucleus retinoate receptor mRNA modulation retinoid
IT Animal cell line
(S91-C2 melanoma, mRNA for nuclear retinoic acid receptors of, retinoids modulation of)

=> d ibib abs kwic 1-16

L18 ANSWER 1 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:88534 CA
TITLE: Electrophysiological and pharmacological analysis of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in the rat
AUTHOR(S): Ezure, Kazuhisa; Tanaka, Ikuko; Miyazaki, Makoto
CORPORATE SOURCE: Department of Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Fuchu, Tokyo, 183-8526, Japan
SOURCE: Experimental Brain Research (1999), 128(4), 471-480
CODEN: EXBRAP; ISSN: 0014-4819
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The information from pulmonary rapidly adapting stretch receptors (RARs) to the central nervous system (CNS) is relayed in the nucleus tractus solitarii (NTS). The second-order neurons in the NTS referred to as RAR cells have recently been shown to receive rhythmic inputs from

the central respiratory system in addn. to the main inputs from **RAR** afferents. The present study analyzed these synaptic inputs by intracellular recordings from **RAR** cells, and by extracellular recordings combined with local applications of neuroactive drugs to **RAR** cells, in Nembutal-anesthetized, paralyzed, and artificially ventilated rats. The intracellular anal. identified both excitatory postsynaptic potentials (EPSPs) elicited presumably by **RAR** afferents and inhibitory postsynaptic potentials (IPSPs) synchronous with central inspiratory activity. This inhibitory input, called I suppression, was the origin of respiratory **modulation** of **RAR** cell firing, and its time course suggested that some unidentified inspiratory neurons with an augmenting firing pattern were the source of the inhibition. The pharmacol. anal. suggested the types of neurotransmitters used in these synaptic events. First, glutamate was shown to be the primary neurotransmitter at the synapse between **RAR** afferents and **RAR** cells. Iontophoretic applications of the non-NMDA glutamate antagonist, CNQX, abolished **RAR** cell firing almost completely in response to lung inflation and deflation and to elec. stimulation of the vagus nerve. Second, glycinergic inputs which inhibited **RAR** cells in the inspiratory phase were revealed by applications of the glycine antagonist, strychnine. I.e., the I suppression was greatly diminished by applications of strychnine. Third, although applications of the GABAA receptor antagonist, bicuculline, had little effect on I suppression, bicuculline markedly increased the baseline firing of **RAR** cells. These results imply that the information path from **RARs** to the CNS is regulated at the level of **RAR** cells by phasically-acting glycinergic inhibition in the inspiratory phase and tonically-acting GABAergic inhibition; the results also provide new insights into the neuronal mechanisms of **RAR**-induced reflexes.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Experimental Brain Research (1999), 128(4), 471-480
CODEN: EXBRAP; ISSN: 0014-4819

AB The information from pulmonary rapidly adapting stretch receptors (**RARs**) to the central nervous system (CNS) is relayed in the nucleus tractus solitarii (NTS). The second-order neurons in the NTS referred to as **RAR** cells have recently been shown to receive rhythmic inputs from the central respiratory system in addn. to the main inputs from **RAR** afferents. The present study analyzed these synaptic inputs by intracellular recordings from **RAR** cells, and by extracellular recordings combined with local applications of neuroactive drugs to **RAR** cells, in Nembutal-anesthetized, paralyzed, and artificially ventilated rats. The intracellular anal. identified both excitatory postsynaptic potentials (EPSPs) elicited presumably by **RAR** afferents and inhibitory postsynaptic potentials (IPSPs) synchronous with central inspiratory activity. This inhibitory input, called I suppression, was the origin of respiratory **modulation** of **RAR** cell firing, and its time course suggested that some unidentified inspiratory neurons with an augmenting firing pattern were the source of the inhibition. The pharmacol. anal. suggested the types of neurotransmitters used in these synaptic events. First, glutamate was shown to be the primary neurotransmitter at the synapse between **RAR** afferents and **RAR** cells. Iontophoretic applications of the non-NMDA glutamate antagonist, CNQX, abolished **RAR** cell firing almost completely in response to lung inflation and deflation and to elec. stimulation of the vagus nerve. Second, glycinergic inputs which inhibited **RAR** cells in the inspiratory phase were revealed by applications of the glycine antagonist, strychnine. I.e., the I suppression was greatly diminished by applications of

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IT **Lung**
Reflex
Synapse

(electrophysiol. and pharmacol. anal. of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in rat)

IT **Breathing** (animal)

(inspiratory phase; electrophysiol. and pharmacol. anal. of synaptic inputs to pulmonary rapidly adapting receptor relay neurons in rat)

L18 ANSWER 2 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 132:88293 CA

TITLE: Retinoic acid: its metabolism and mechanism of action

AUTHOR(S): Kwiatkowska, Danuta; Kwiatkowska-Korczak, Janina

CORPORATE SOURCE: Zaklad Biochem, Akad. Med., Wroclaw, Pol.

SOURCE: Postepy Biologii Komorki (1999), 26(3), 579-592

CODEN: PBKODV; ISSN: 0324-833X

PUBLISHER: Fundacja Biologii Komorki i Biologii Molekularnej

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Polish

AB A review with 91 refs. Retinoic acid, a potent morphogen, regulates cell growth and differentiation in embryo and adults. Also, it **modulates** function of many hormones and enzymes. In liver it is derived from carotene, in other tissues - from retinol. Retinoic acid is present as all-trans, 9-cis and 13-cis isoforms. In cytoplasm they are bound by proteins CRABP I and II. Nuclear receptors of retinoic acid, **RAR** and RXR, belong to the superfamily of ligand inducible transcription factors, that include receptors of steroid hormones, thyroxine and vitamin D. Receptors of the **RAR** class interact with all retinoic acid isomers, RXR - with 9-cis-form only. Three isoforms - .alpha., .beta. and .chi. - of both classes are present in cells. Only heterodimer **RAR/RXR** is biol. active. It is bound to the response elements in DNA, consisting of two AGGTCA direct repeats, sepd. by two or five nucleotides. This interaction stimulates transactivity function of the receptor, resulting in induction or repression of target genes. Modifications of the receptor isoform presence and localization, for instance lack of **RAR**.beta., was found in many tumors. Growth inhibition and differentiation induction was obsd. after retinoid treatment in leukemic, breast and lung cancer, teratocarcinoma and other malignant tissues.

SO Postepy Biologii Komorki (1999), 26(3), 579-592

CODEN: PBKODV; ISSN: 0324-833X

AB A review with 91 refs. Retinoic acid, a potent morphogen, regulates cell growth and differentiation in embryo and adults. Also, it **modulates** function of many hormones and enzymes. In liver it is derived from carotene, in other tissues - from retinol. Retinoic acid is present as all-trans, 9-cis and 13-cis isoforms. In cytoplasm they are bound by proteins CRABP I and II. Nuclear receptors of retinoic acid, **RAR** and RXR, belong to the superfamily of ligand inducible transcription factors, that include receptors of steroid hormones, thyroxine and vitamin D. Receptors of the **RAR** class interact with all retinoic acid isomers, RXR - with 9-cis-form only. Three

09/919,195

isoforms - .alpha., .beta. and .chi. - of both classes are present in cells. Only heterodimer **RAR/RXR** is biol. active. It is bound to the response elements in DNA, consisting of two AGGTCA direct repeats, sepd. by two or five nucleotides. This interaction stimulates transactivity function of the receptor, resulting in induction or repression of target genes. Modifications of the receptor isoform presence and localization, for instance lack of **RAR.beta.**, was found in many tumors. Growth inhibition and differentiation induction was obsd. after retinoid treatment in leukemic, breast and lung cancer, teratocarcinoma and other malignant tissues.

ST review retinoate metab **RAR RXR** cell proliferation; retinoic acid receptor cell differentiation tumor review

L18 ANSWER 3 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 132:87849 CA

TITLE: Nuclear retinoid acid receptor beta in bronchial epithelium of smokers before and during chemoprevention

AUTHOR(S): Xu, Xiao-Chun; Lee, Jin S.; Lee, J. Jack; Morice, Rodolfo C.; Liu, Xiaoming; Lippman, Scott M.; Hong, Waun K.; Lotan, Reuben

CORPORATE SOURCE: Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Journal of the National Cancer Institute (1999), 91(15), 1317-1321

CODEN: JNCIEQ; ISSN: 0027-8874

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Retinoids can reverse neoplastic lesions and prevent second primary tumors in the aerodigestive tract. These effects are thought to be mediated by nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each receptor group including three subtypes (.alpha., .beta., and .gamma.). Previously, we found that **RAR.beta.** expression was suppressed in lung cancer. In this study, we investigated whether expression of **RAR.beta.** is modulated by chemopreventive intervention. Methods: Using in situ hybridization, we analyzed **RAR.beta.** mRNA (mRNA) expression in bronchial biopsy specimens from heavy smokers, at baseline and after 6 mo of treatment with 13-cis-retinoic acid (13-cis-RA) or placebo. Since we had previously detected **RAR.beta.** expression in 90% of bronchial specimens from nonsmokers, we considered loss of **RAR.beta.** mRNA expression in at least one of six biopsy specimens at baseline in this study to be aberrant. Results: **RAR.beta.** mRNA expression was aberrant in 30 (85.7%) of 35 subjects in the 13-cis-RA group and in 24 (72.7%) of 33 subjects in the placebo group. After 6 mo of 13-cis-RA treatment, the no. of subjects who were **RAR.beta.** pos. in all six biopsy specimens increased from five of 35 to 13 of 35 (2.6-fold), so that the percentage of individuals with aberrant **RAR.beta.** expression decreased to 62.9% (22 of 35), which represents a statistically significant difference from baseline expression (two-sided P = .01). In the placebo group, no statistically significant difference in **RAR.beta.** expression was obsd. between baseline and 6 mo. **RAR.beta.** expression was not related to current smoking status or reversal of squamous metaplasia. Conclusions: These results indicate that **RAR.beta.** is an independent marker of response to 13-cis-RA and may serve as an intermediate biomarker in chemoprevention trials of upper aerodigestive tract cancers.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

- SO Journal of the National Cancer Institute (1999), 91(15), 1317-1321
CODEN: JNCIEQ; ISSN: 0027-8874
- AB Background: Retinoids can reverse neoplastic lesions and prevent second primary tumors in the aerodigestive tract. These effects are thought to be mediated by nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each receptor group including three subtypes (.alpha., .beta., and .gamma.). Previously, we found that **RAR.beta.** expression was suppressed in lung cancer. In this study, we investigated whether expression of **RAR.beta.** is modulated by chemopreventive intervention. Methods: Using in situ hybridization, we analyzed **RAR.beta.** mRNA (mRNA) expression in bronchial biopsy specimens from heavy smokers, at baseline and after 6 mo of treatment with 13-cis-retinoic acid (13-cis-RA) or placebo. Since we had previously detected **RAR.beta.** expression in 90% of bronchial specimens from nonsmokers, we considered loss of **RAR.beta.** mRNA expression in at least one of six biopsy specimens at baseline in this study to be aberrant. Results: **RAR.beta.** mRNA expression was aberrant in 30 (85.7%) of 35 subjects in the 13-cis-RA group and in 24 (72.7%) of 33 subjects in the placebo group. After 6 mo of 13-cis-RA treatment, the no. of subjects who were **RAR.beta.** pos. in all six biopsy specimens increased from five of 35 to 13 of 35 (2.6-fold), so that the percentage of individuals with aberrant **RAR.beta.** expression decreased to 62.9% (22 of 35), which represents a statistically significant difference from baseline expression (two-sided P = .01). In the placebo group, no statistically significant difference in **RAR.beta.** expression was obsd. between baseline and 6 mo. **RAR.beta.** expression was not related to current smoking status or reversal of squamous metaplasia. Conclusions: These results indicate that **RAR.beta.** is an independent marker of response to 13-cis-RA and may serve as an intermediate biomarker in chemoprevention trials of upper aerodigestive tract cancers.
- ST **RAR** bronchial epithelium smoker retinoic acid; retinoic acid biomarker chemoprevention lung cancer
- IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**RAR-.beta.**; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Diagnosis
(cancer; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Chemotherapy
(chemoprevention; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Neoplasm
(diagnosis; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Bronchi
(epithelium; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Antitumor agents
Biomarkers (biological responses)
Tobacco smoke
(nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)
- IT Cell proliferation
(squamous metaplasia; nuclear **RAR-.beta.** in bronchial epithelium of smokers before and during chemoprevention)

09/919,195

IT Lung

(type I cell, metaplasia; nuclear RAR-.beta. in bronchial epithelium of smokers before and during chemoprevention)

IT 4759-48-2, 13-cis-Retinoic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(nuclear RAR-.beta. in bronchial epithelium of smokers before and during chemoprevention)

L18 ANSWER 4 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 132:58791 CA

TITLE: Retinoid-mediated suppression of tumor invasion and matrix metalloproteinase synthesis

AUTHOR(S): Schoenermark, Matthias P.; Mitchell, Teresa I.; Rutter, Joni L.; Reczek, Peter R.; Brinckerhoff, Constance E.

CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, 03755, USA

SOURCE: Annals of the New York Academy of Sciences (1999), 878(Inhibition of Matrix Metalloproteinases), 466-486
CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cancer mortality usually results from the tumor invading the local environment and metastasizing to vital organs, e.g. liver, lung, and brain. Degrtn. of the extracellular matrix is, therefore, the sine qua non of tumor cell invasion, this degrdn. is mediated mainly by MMPs, and thus, inhibition of MMP synthesis is a target for anticancer agents. Tumor cells must traverse both the basement membrane (type IV collagen) and the interstitial stroma (type I collagen). Therefore, we used SEM to examine the invasive behavior of several aggressive tumor cell lines, A2058 melanoma cells, and SCC and FaDu squamous cell carcinomas through these matrixes; and we monitored the ability of all-trans retinoic acid and several RAR-specific ligands to block invasion. We demonstrate that several retinoids, which are specific RAR .alpha., .beta., or .gamma. agonists/antagonists, selectively inhibited MMP synthesis in the three tumor cell lines. However, there was not a common pattern of MMP inhibition by a particular retinoid. For instance, a RAR.alpha. antagonist suppressed MMP-1 and MMP-2 synthesis in the melanoma cell line, but not in the FaDu or SCC-25 cells. On the other hand, synthesis of MMP-1 and MMP-9 by the FaDu cells was affected hardly at all, while a RAR.gamma. antagonist reduced the levels of MMP-2. Only all-trans retinoic acid reduced MMP-1 synthesis in these cells. We postulate that the differences may be related to a differential pattern of RAR expression in each of these cells, and that the RARs expressed by each cell line may not be targets of these RAR specific compds. All-trans retinoic acid is a pan ligand, binding to all three RARs and, therefore, may modulate gene expression more generally. We conclude that the power of these new ligands lies in their specificity, which can be directed towards modulating expression of certain RARs and, thus, of certain MMPs. By blocking MMP synthesis, retinoids may be effective in cancer therapy by decreasing tumor invasiveness.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Annals of the New York Academy of Sciences (1999),
878(Inhibition of Matrix Metalloproteinases), 466-486
CODEN: ANYAA9; ISSN: 0077-8923

09/919,195

AB Cancer mortality usually results from the tumor invading the local environment and metastasizing to vital organs, e.g. liver, lung, and brain. Degrn. of the extracellular matrix is, therefore, the sine qua non of tumor cell invasion, this degn. is mediated mainly by MMPs, and thus, inhibition of MMP synthesis is a target for anticancer agents. Tumor cells must traverse both the basement membrane (type IV collagen) and the interstitial stroma (type I collagen). Therefore, we used SEM to examine the invasive behavior of several aggressive tumor cell lines, A2058 melanoma cells, and SCC and FaDu squamous cell carcinomas through these matrixes; and we monitored the ability of all-trans retinoic acid and several **RAR**-specific ligands to block invasion. We demonstrate that several retinoids, which are specific **RAR** .alpha., .beta., or .gamma. agonists/antagonists, selectively inhibited MMP synthesis in the three tumor cell lines. However, there was not a common pattern of MMP inhibition by a particular retinoid. For instance, a **RAR**.alpha. antagonist suppressed MMP-1 and MMP-2 synthesis in the melanoma cell line, but not in the FaDu or SCC-25 cells. On the other hand, synthesis of MMP-1 and MMP-9 by the FaDu cells was affected hardly at all, while a **RAR**.gamma. antagonist reduced the levels of MMP-2. Only all-trans retinoic acid reduced MMP-1 synthesis in these cells. We postulate that the differences may be related to a differential pattern of **RAR** expression in each of these cells, and that the **RAR**s expressed by each cell line may not be targets of these **RAR** specific compds. All-trans retinoic acid is a pan ligand, binding to all three **RAR**s and, therefore, may **modulate** gene expression more generally. We conclude that the power of these new ligands lies in their specificity, which can be directed towards **modulating** expression of certain **RAR**s and, thus, of certain MMPs. By blocking MMP synthesis, retinoids may be effective in cancer therapy by decreasing tumor invasiveness.

ST antitumor antimetastatic retinoid MMP synthesis inhibitor; **RAR** extracellular matrix retinoate melanoma inhibitor; head neck carcinoma MMP retinoid receptor

IT Retinoic acid receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**RAR**-.alpha.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

IT Retinoic acid receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**RAR**-.beta.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

IT Retinoic acid receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**RAR**-.gamma.; retinoid-mediated suppression of tumor invasion and MMP synthesis)

L18 ANSWER 5 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 131:295601 CA

TITLE: Means for the **modulation** of processes mediated by retinoid receptors, compounds useful therefor, preparation of compounds, and therapeutic use

INVENTOR(S): Evans, Ronald M.; Mangelsdorf, David J.; Heyman, Richard A.; Boehm, Marcus F.; Bichele, Gregor; Thaller, Christina

PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA; Baylor College of Medicine; Ligand Pharmaceuticals, Inc.

09/919,195

SOURCE: U.S., 25 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968989	A	19991019	US 1995-472817	19950607 <--
PRIORITY APPLN. INFO.:			US 1995-472817	19950607

OTHER SOURCE(S): MARPAT 131:295601

AB Methods are provided to **modulate** processes mediated by retinoid receptors, employing high affinity, high specificity ligands for such receptors. The invention provides ligands which are more selective for the retinoid X receptor than is retinoic acid (i.e., retinoids). In another aspect of the invention, alternative ligands (other than retinoic acid) have been discovered which are capable of inducing retinoic acid receptor mediated processes. In yet another aspect, methods have been developed for the prepn. of such retinoid receptor ligands from readily available compds. The compds. are useful therapeutically for e.g. treatment of nonmalignant and malignant skin disorders.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Means for the **modulation** of processes mediated by retinoid receptors, compounds useful therefor, preparation of compounds, and therapeutic use

PI US 5968989 A 19991019

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968989	A	19991019	US 1995-472817	19950607 <--

AB Methods are provided to **modulate** processes mediated by retinoid receptors, employing high affinity, high specificity ligands for such receptors. The invention provides ligands which are more selective for the retinoid X receptor than is retinoic acid (i.e., retinoids). In another aspect of the invention, alternative ligands (other than retinoic acid) have been discovered which are capable of inducing retinoic acid receptor mediated processes. In yet another aspect, methods have been developed for the prepn. of such retinoid receptor ligands from readily available compds. The compds. are useful therapeutically for e.g. treatment of nonmalignant and malignant skin disorders.

IT Apolipoproteins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(A-I; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(CRABP (cellular retinoic acid-binding protein); **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Animal cell line

(F9; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)

IT Retinoic acid receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(RAR-.alpha.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and

- therapeutic use)
- IT Retinoic acid receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (RAR-.beta.; **modulation** of processes mediated by
 retinoid receptors, compds. useful therefor, compd. prepn., and
 therapeutic use)
- IT Retinoic acid receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (RAR-.gamma.; **modulation** of processes mediated by
 retinoid receptors, compds. useful therefor, compd. prepn., and
 therapeutic use)
- IT Retinoid X receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (RXR.alpha.; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Retinoid X receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (RXR.beta.; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Retinoid X receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (RXR.gamma.; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Drosophila melanogaster
 (Schneider cell line (S2); **modulation** of processes mediated
 by retinoid receptors, compds. useful therefor, compd. prepn., and
 therapeutic use)
- IT Transcriptional regulation
 (activation; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
 (acute promyelocytic leukemia; **modulation** of processes
 mediated by retinoid receptors, compds. useful therefor, compd. prepn.,
 and therapeutic use)
- IT Aging, animal
 (and wrinkles; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
 (carcinoma; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Cell proliferation
 (disorder; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Lung, neoplasm
 Lung, neoplasm
 Skin, neoplasm
 Skin, neoplasm
 Testis, neoplasm
 Testis, neoplasm
 (inhibitors; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Skin, disease
 (keratinization; **modulation** of processes mediated by retinoid
 receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Skin

- (keratinocyte; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
Antitumor agents
(lung; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
(melanoma; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Acne
Antitumor agents
Cell differentiation
Drug delivery systems
Skin
Skin, disease
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Retinoic acid receptors
Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
(promyelocytic leukemia; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
Antitumor agents
(skin; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Drug interactions
(synergistic; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Antitumor agents
Antitumor agents
(testis; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; **modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 302-79-4, all-trans-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**modulation** of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 5300-03-8P, 9-cis-Retinoic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**modulation** of processes mediated by retinoid receptors,

- comps. useful therefor, compd. prepn., and therapeutic use)
- IT 150737-17-0P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study; unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (modulation of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 150643-13-3P 150737-18-1P, 4-keto-9-cis-Retinoic acid
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study; unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (modulation of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 150907-24-7P 151004-87-4P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. and reaction; modulation of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 39760-56-0 150907-23-6
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (reaction; modulation of processes mediated by retinoid receptors, compds. useful therefor, compd. prepn., and therapeutic use)
- IT 149958-05-4
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; means for the modulation of processes mediated by retinoid receptors, compds. useful therefor, prepn. of compds., and therapeutic use)
- IT 247116-03-6, PN: US5968989 SEQID: 1 unclaimed protein
 RL: PRP (Properties)
 (unclaimed protein sequence; means for the modulation of processes mediated by retinoid receptors, compds. useful therefor, prepn. of compds., and therapeutic use)

L18 ANSWER 6 OF 16 CA COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 131:168353 CA
 TITLE: Identification of loci involved in accelerated wound healing and the development of new wound healing promoters
 INVENTOR(S): Heber-Katz, Ellen
 PATENT ASSIGNEE(S): The Wistar Institute, USA
 SOURCE: PCT Int. Appl., 136 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941364	A2	19990819	WO 1999-US2962	19990212 <--
WO 9941364	A3	19991223		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,			

09/919,195

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2319700 AA 19990819 CA 1999-2319700 19990212 <--
AU 9926720 A1 19990830 AU 1999-26720 19990212 <--
EP 1053309 A1 20001122 EP 1999-906924 19990212

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

JP 2002503460 T2 20020205 JP 2000-531545 19990212
US 2003037345 A1 20030220 US 1999-249155 19990212

PRIORITY APPLN. INFO.:
US 1998-74737P A2 19980213
US 1998-97937P A2 19980826
US 1998-102051P A2 19980928
WO 1999-US2962 W 19990212

AB Genes that quant. improve the efficiency and effectiveness of wound
healing in mice are identified. Wound healing is assayed by measuring the
time taken for a 2 mm hole punched into the ear to heal. The genes or
gene products may be useful in the development of new wound healing
promoters, including agents for treatment of central and peripheral nerve
wounds. Wound healing in the rapidly healing mouse line MRL was studied.
In comparison to the C57BL/6 line, the MRL mice showed more extensive
vascularization around wounds with rapid development of sebaceous glands
and hair follicles and the unexpected appearance of adipocytes. These
mice also showed improved healing of damage to the optic and sciatic nerve
after crushing, and of the spinal cord after complete transection. Using
the difference in wound healing behavior of the two lines, genetic
polymorphisms assocd. with QTLs affecting wound healing were identified.
The accelerated healing of the MRL line was lost with aging, and this
appeared to be as a result of T-cell actions. Macrophages from the MRL
accelerated wound healing in control mice.

PI WO 9941364 A2 19990819

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941364	A2	19990819	WO 1999-US2962	19990212 <--
WO 9941364	A3	19991223		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2319700 AA 19990819 CA 1999-2319700 19990212 <--
AU 9926720 A1 19990830 AU 1999-26720 19990212 <--
EP 1053309 A1 20001122 EP 1999-906924 19990212

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

JP 2002503460 T2 20020205 JP 2000-531545 19990212
US 2003037345 A1 20030220 US 1999-249155 19990212

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LKLF (lung Kruppel-like zinc finger transcription factor),
gene for, expression in healing wounds of; identification of loci
involved in accelerated wound healing and development of new wound
healing promoters)

IT Retinoic acid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RAR-.gamma., gene for, expression in healing wounds of;
identification of loci involved in accelerated wound healing and

09/919,195

- development of new wound healing promoters)
- IT Apoptosis
Cell adhesion
Cell migration
Cell proliferation
Transcription, genetic
Translation, genetic
(modulation of, in acceleration of wound healing;
identification of loci involved in accelerated wound healing and
development of new wound healing promoters)
- IT DNA formation
(replication, modulation of, in acceleration of wound
healing; identification of loci involved in accelerated wound healing
and development of new wound healing promoters)

L18 ANSWER 7 OF 16 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:69157 CA
TITLE: Inhibition of hSP-B promoter in respiratory epithelial
cells by a dominant negative retinoic acid receptor
AUTHOR(S): Ghaffari, Manely; Whitsett, Jeffrey A.; Yan, Cong
CORPORATE SOURCE: Division of Pulmonary Biology, Children's Hospital
Medical Center, Cincinnati, OH, 45229-3039, USA
SOURCE: American Journal of Physiology (1999),
276(3, Pt. 1), L398-L404
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinoic acid (RA) receptors (RARs) belong to the nuclear hormone receptor superfamily and play important roles in lung differentiation, growth, and gene regulation. Surfactant protein (SP) B is a small hydrophobic protein synthesized and secreted by respiratory epithelial cells in the lung. Expression of the SP-B gene is modulated at the transcriptional and posttranscriptional levels. In the present work, immunohistochem. staining revealed that RAR-.alpha. is present on day 14.5 of gestation in the fetal mouse lung. To assess whether RAR is required for SP-B gene transcription, a dominant neg. mutant human (h) RAR-.alpha.403 was generated. The hRAR-.alpha.403 mutant was transcribed and translated into the truncated protein product by reticulocyte lysate in vitro. The mutant retained DNA binding activity in the presence of retinoid X receptor-.gamma. to an RA response element in the hSP-B promoter. When transiently transfected into pulmonary adenocarcinoma epithelial cells (H441 cells), the mutant hRAR-.alpha.403 was readily detected in the cell nucleus. Cotransfection of the mutant hRAR-.alpha.403 repressed activity of the hSP-B promoter and inhibited RA-induced surfactant proprotein B prodn. in H441 cells, supporting the concept that RAR is required for hSP-B gene transcription in vitro.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

- SO American Journal of Physiology (1999), 276(3, Pt. 1), L398-L404
CODEN: AJPHAP; ISSN: 0002-9513
- AB Retinoic acid (RA) receptors (RARs) belong to the nuclear hormone receptor superfamily and play important roles in lung differentiation, growth, and gene regulation. Surfactant protein (SP) B is a small hydrophobic protein synthesized and secreted by respiratory epithelial cells in the lung. Expression of the SP-B gene is modulated at the transcriptional and posttranscriptional levels. In the present work, immunohistochem. staining revealed that RAR-.alpha. is present on day 14.5 of gestation in the fetal mouse

lung. To assess whether **RAR** is required for SP-B gene transcription, a dominant neg. mutant human (h) **RAR-.alpha.403** was generated. The h**RAR-.alpha.403** mutant was transcribed and translated into the truncated protein product by reticulocyte lysate in vitro. The mutant retained DNA binding activity in the presence of retinoid X receptor-.gamma. to an RA response element in the hSP-B promoter. When transiently transfected into pulmonary adenocarcinoma epithelial cells (H441 cells), the mutant h**RAR-.alpha.403** was readily detected in the cell nucleus. Cotransfection of the mutant h**RAR-.alpha.403** repressed activity of the hSP-B promoter and inhibited RA-induced surfactant proprotein B prodn. in H441 cells, supporting the concept that **RAR** is required for hSP-B gene transcription in vitro.

ST SP B gene promoter transcription retinoate receptor **lung**
 IT Retinoic acid receptors
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (**RAR-.alpha.**; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)
)

IT Gene, animal
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (SP-B; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Surfactant proteins (pulmonary)
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (SP-B; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Transcriptional regulation
 (activation; retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT **Lung**
 (retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

IT Promoter (genetic element)
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (retinoic acid receptor .alpha. in transcription activation of human surfactant protein B gene promoter in **lung**)

L18 ANSWER 8 OF 16 CA COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 130:50438 CA
 TITLE: Retinoid receptors and cancer
 AUTHOR(S): Fontana, Joseph A.; Rishi, Arun K.
 CORPORATE SOURCE: Department of Medicine and Cancer Center, University of Maryland at Baltimore, Baltimore, MD, USA
 SOURCE: Advances in Organ Biology (1997),
 3(Retinoids: Their Physiological Function and Therapeutic Potential), 219-230
 CODEN: AOBIFW
 PUBLISHER: JAI Press Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review, with 66 refs. Retinoids display therapeutic efficacy in a no. of premalignant and malignant diseases. Retinoids **modulate** cellular phenotypes by binding to a no. of retinoic acid nuclear receptors (**RAR.alpha.**, **.beta.**, or **.gamma.**) or retinoic X nuclear receptors (**RXR.alpha.**, **.beta.** or **.gamma.**). Most cells express more than one

09/919,195

RAR and **RXR** receptor. Various **RAR** and **RXR** subtypes activate different and distinct genes by binding to specific retinoid response elements located in the regulatory regions of target genes. **Modulation** of the expression of these receptors has a profound effect on the physiol. of the cells and their acquisition of a malignant phenotype. **RAR.alpha.** appears to regulate hematopoietic differentiation and its loss of mutation results in aberrant growth. **RAR.beta.** is expressed in both normal lung and breast tissue while **RAR.beta.** expression is lost in their malignant counterparts. The mechanism(s) involved in the loss of **RAR .beta.** in these tissues is unclear. Finally, **RAR.alpha.** expression in breast carcinoma is regulated by the estrogen receptor and its presence is necessary for the retinoic acid-mediated inhibition of growth.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Advances in Organ Biology (1997), 3(Retinoids: Their Physiological Function and Therapeutic Potential), 219-230
CODEN: AOBIFW

AB A review, with 66 refs. Retinoids display therapeutic efficacy in a no. of premalignant and malignant diseases. Retinoids **modulate** cellular phenotypes by binding to a no. of retinoic acid nuclear receptors (**RAR.alpha.**, **.beta.**, or **.gamma.**) or retinoic X nuclear receptors (**RXR.alpha.**, **.beta.** or **.gamma.**). Most cells express more than one **RAR** and **RXR** receptor. Various **RAR** and **RXR** subtypes activate different and distinct genes by binding to specific retinoid response elements located in the regulatory regions of target genes. **Modulation** of the expression of these receptors has a profound effect on the physiol. of the cells and their acquisition of a malignant phenotype. **RAR.alpha.** appears to regulate hematopoietic differentiation and its loss of mutation results in aberrant growth. **RAR.beta.** is expressed in both normal lung and breast tissue while **RAR.beta.** expression is lost in their malignant counterparts. The mechanism(s) involved in the loss of **RAR .beta.** in these tissues is unclear. Finally, **RAR.alpha.** expression in breast carcinoma is regulated by the estrogen receptor and its presence is necessary for the retinoic acid-mediated inhibition of growth.

L18 ANSWER 9 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 129:258278 CA

TITLE: Retinoic acid-receptor activation of SP-B gene transcription in respiratory epithelial cells

AUTHOR(S): Yan, Cong; Ghaffari, Manely; Whitsett, Jeffrey A.; Zeng, Xin; Sever, Zvezdana; Lin, Sui

CORPORATE SOURCE: Division of Pulmonary Biology, Children's Hospital Medical Center, Cincinnati, OH, 45229-3039, USA

SOURCE: American Journal of Physiology (1998), 275(2, Pt. 1), L239-L246
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Retinoids are known to play important roles in organ development of the lung. Retinoids exert their activity by **modulating** the expression of numerous genes, generally influencing gene transcription, in target cells. In the present work, the mechanism by which retinoic acid (RA) regulates surfactant protein (SP) B expression was assessed in vitro. RA (9-cis-RA) enhanced SP-B mRNA in pulmonary adenocarcinoma cells (H441 cells) and increased transcriptional activity of the SP-B promoter in both

H441 and mouse **lung** epithelial cells (MLE-15). Cotransfection of H441 cells with retinoid nuclear receptor (RAR)-.alpha., -.beta., and -.gamma. and retinoid X receptor (RXR)-.gamma. further increased the response of the SP-B promoter to RA. Treatment of H441 cells with RA increased immunostaining for the SP-B proprotein and increased the no. of cells in which the SP-B proprotein was detected. An RA responsive element mediating RA stimulating of the human SP-B promoter was identified. RAR-.alpha. and -.gamma. and RXR-.alpha. but not RAR-.beta. or RXR-.beta. and -.gamma. were detected by immunohistochem. anal. of H441 cells. RA, by activating RAR activity, stimulated the transcription and synthesis of SP-B in pulmonary adenocarcinoma cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

- SO American Journal of Physiology (1998), 275(2, Pt. 1), L239-L246
CODEN: AJPHAP; ISSN: 0002-9513
- AB Retinoids are known to play important roles in organ development of the **lung**. Retinoids exert their activity by **modulating** the expression of numerous genes, generally influencing gene transcription, in target cells. In the present work, the mechanism by which retinoic acid (RA) regulates surfactant protein (SP) B expression was assessed in vitro. RA (9-cis-RA) enhanced SP-B mRNA in pulmonary adenocarcinoma cells (H441 cells) and increased transcriptional activity of the SP-B promoter in both H441 and mouse **lung** epithelial cells (MLE-15). Cotransfection of H441 cells with retinoid nuclear receptor (RAR)-.alpha., -.beta., and -.gamma. and retinoid X receptor (RXR)-.gamma. further increased the response of the SP-B promoter to RA. Treatment of H441 cells with RA increased immunostaining for the SP-B proprotein and increased the no. of cells in which the SP-B proprotein was detected. An RA responsive element mediating RA stimulating of the human SP-B promoter was identified. RAR-.alpha. and -.gamma. and RXR-.alpha. but not RAR-.beta. or RXR-.beta. and -.gamma. were detected by immunohistochem. anal. of H441 cells. RA, by activating RAR activity, stimulated the transcription and synthesis of SP-B in pulmonary adenocarcinoma cells.
- ST SPB transcription activation retinoate receptor **lung**;
lung adenocarcinoma SPA SPC transcription activation
- IT **Lung**, neoplasm
(adenocarcinoma; retinoic acid-receptor activation of SP-B gene transcription in respiratory epithelial cells)

L18 ANSWER 10 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 129:225149 CA
TITLE: Retinoic acid inhibits growth and enhances differentiation of testicular carcinoma cells
AUTHOR(S): Ueno, Munehisa; Deguchi, Nobuhiro
CORPORATE SOURCE: Department of Urology, Kidney Disease Center, Saitama Medical School, Japan
SOURCE: Molecular Urology (1998), 2(2), 49-55
CODEN: MOURFE; ISSN: 1091-5362
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB This review with 32 refs. summarizes our recent studies on the roles played by retinoic acid compds. in cell growth and differentiation of testicular cancers. In these cells, differentiation involves the prodn. of alpha-fetoprotein (AFP), which is known as extraembryonic differentiation. Very recently, we have established a testicular carcinoma cell line, KU-MT, from a **lung** metastasis. The KU-MT cells expressed the retinoic acid receptors (RAR)-.alpha. and

- RAR-.gamma.**, and **RXR-.alpha.** These RARs were upregulated in response to treatment with all-trans-retinoic acid (ATRA). Alpha-fetoprotein is continuously produced by these cells, whether they are grown in culture or as xenografts in nude mice. Treatments with ATRA caused elevation of AFP prodn. and inhibited the growth of KU-MT cells in vitro. The compd. also arrested the cell cycle in G1 and reduced the percentage of S-phase cells assocd. with wild-type p53, leading to a modest induction of apoptosis. The wild-type p53 protein may mediate the cell cycle and induce apoptosis when the cells differentiated. All-trans-retinoic acid and **RAR-.alpha.**-specific agonists upregulated the expression of laminin, a marker of endoderm differentiation, and the expression of 45 kDa bone morphogenetic protein-2, whereas arotinoid, which is not bound to **RAR-.alpha.**, did not show any effects. In summary, retinoic acid compds. could **modulate** cell growth and differentiation of testicular cancers through their assocn. with **RAR-.alpha.**
- SO Molecular Urology (1998), 2(2), 49-55
CODEN: MOURFE; ISSN: 1091-5362
- AB This review with 32 refs. summarizes our recent studies on the roles played by retinoic acid compds. in cell growth and differentiation of testicular cancers. In these cells, differentiation involves the prodn. of alpha-fetoprotein (AFP), which is known as extraembryonic differentiation. Very recently, we have established a testicular carcinoma cell line, KU-MT, from a lung metastasis. The KU-MT cells expressed the retinoic acid receptors (**RAR**)-.alpha. and **RAR**-.gamma., and **RXR**-.alpha.. These RARs were upregulated in response to treatment with all-trans-retinoic acid (ATRA). Alpha-fetoprotein is continuously produced by these cells, whether they are grown in culture or as xenografts in nude mice. Treatments with ATRA caused elevation of AFP prodn. and inhibited the growth of KU-MT cells in vitro. The compd. also arrested the cell cycle in G1 and reduced the percentage of S-phase cells assocd. with wild-type p53, leading to a modest induction of apoptosis. The wild-type p53 protein may mediate the cell cycle and induce apoptosis when the cells differentiated. All-trans-retinoic acid and **RAR**-.alpha.-specific agonists upregulated the expression of laminin, a marker of endoderm differentiation, and the expression of 45 kDa bone morphogenetic protein-2, whereas arotinoid, which is not bound to **RAR**-.alpha., did not show any effects. In summary, retinoic acid compds. could **modulate** cell growth and differentiation of testicular cancers through their assocn. with **RAR**-.alpha..

L18 ANSWER 11 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 127:16087 CA
TITLE: Suppression of retinoic acid receptor .beta. in non-small-cell lung cancer in vivo: implications for lung cancer development
AUTHOR(S): Xu, Xiao-Chun; Sozzi, Gabriella; Lee, Jin S.; Lee, J. Jack; Pastorino, Ugo; Pilotti, Silvana; Kurie, Jonathan M.; Hong, Waun K.; Lotan, Reuben
CORPORATE SOURCE: Departments of Tumor Biology and Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Journal of the National Cancer Institute (1997), 89(9), 624-629
CODEN: JNCIEQ; ISSN: 0027-8874
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Retinoids, analogs of vitamin A, are required for the normal growth and

differentiation of human bronchial epithelium. They are also able to reverse premalignant lesions and prevent second primary tumors in some patients with non-small-cell lung cancer (NSCLC). These effects are thought to result from modulation of cell growth, differentiation, or apoptosis (programmed cell death). When certain retinoid receptors in the cell nucleus, i.e., retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which mediate most retinoid actions are suppressed, abnormal activity may result that could enhance cancer development. This study was designed to det. whether there are abnormalities in the expression of retinoid receptors in surgical specimens from patients with NSCLC. Transcripts of nuclear retinoid receptors were detected in formalin-fixed, paraffin-embedded specimens by use of digoxigenin-labeled riboprobes specific for RAR.alpha., RAR.beta., RAR.gamma., RXR.alpha., RXR.beta., and RXR.gamma. for in situ hybridization to histol. specimens from 79 patients with NSCLC and as control from 17 patients with non-lung cancer. The quality and specificity of the digoxigenin-labeled probes were detd. by northern blotting, and the specificity of the binding of antisense riboprobes was verified by use of sense probes as controls. All receptors were expressed in at least 89% of control normal bronchial tissue specimens from 17 patients without a primary lung cancer and in distant normal bronchus specimens from patients with NSCLC. RAR.alpha., RXR.alpha., and RXR.gamma. were expressed in more than 95% of the NSCLC specimens. In contrast, RAR.beta., RAR.gamma., and RXR.beta. expression was detected in only 42%, 72%, and 76% of NSCLC, resp. Thus, the expression of RAR.alpha., RXR.alpha., and RXR.gamma. is not altered in NSCLC; however, expression of RAR.beta. and possibly also of RAR.gamma. and RXR.beta. is suppressed in a large percentage of patients with lung cancer. The loss of expression of one or more of these nuclear retinoid receptors may be assocd. with lung carcinogenesis.

TI Suppression of retinoic acid receptor .beta. in non-small-cell lung cancer in vivo: implications for lung cancer development

SO Journal of the National Cancer Institute (1997), 89(9), 624-629
CODEN: JNCIEQ; ISSN: 0027-8874

AB Retinoids, analogs of vitamin A, are required for the normal growth and differentiation of human bronchial epithelium. They are also able to reverse premalignant lesions and prevent second primary tumors in some patients with non-small-cell lung cancer (NSCLC). These effects are thought to result from modulation of cell growth, differentiation, or apoptosis (programmed cell death). When certain retinoid receptors in the cell nucleus, i.e., retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which mediate most retinoid actions are suppressed, abnormal activity may result that could enhance cancer development. This study was designed to det. whether there are abnormalities in the expression of retinoid receptors in surgical specimens from patients with NSCLC. Transcripts of nuclear retinoid receptors were detected in formalin-fixed, paraffin-embedded specimens by use of digoxigenin-labeled riboprobes specific for RAR.alpha., RAR.beta., RAR.gamma., RXR.alpha., RXR.beta., and RXR.gamma. for in situ hybridization to histol. specimens from 79 patients with NSCLC and as control from 17 patients with non-lung cancer. The quality and specificity of the digoxigenin-labeled probes were detd. by northern blotting, and the specificity of the binding of antisense riboprobes was verified by use of sense probes as controls. All receptors were expressed in at least 89% of control normal bronchial tissue specimens from 17 patients without a primary lung cancer and in distant normal bronchus specimens from patients with NSCLC. RAR.alpha., RXR.alpha., and RXR.gamma. were expressed in more than 95% of the

NSCLC specimens. In contrast, **RAR.beta.**, **RAR.gamma.**, and **RXR.beta.** expression was detected in only 42%, 72%, and 76% of NSCLC, resp. Thus, the expression of **RAR.alpha.**, **RXR.alpha.**, and **RXR.gamma.** is not altered in NSCLC; however, expression of **RAR.beta.** and possibly also of **RAR.gamma.** and **RXR.beta.** is suppressed in a large percentage of patients with **lung cancer**. The loss of expression of one or more of these nuclear retinoid receptors may be assocd. with **lung carcinogenesis**.

ST **lung cancer retinoate receptor**

IT Retinoic acid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR.alpha.**, mRNA; suppression of retinoic acid receptor
.beta. in human non-small-cell **lung cancer in vivo**)

IT Retinoic acid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR.beta.**, mRNA; suppression of retinoic acid receptor
.beta. in human non-small-cell **lung cancer in vivo**)

IT Retinoic acid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RAR.gamma.**, mRNA; suppression of retinoic acid receptor
.beta. in human non-small-cell **lung cancer in vivo**)

IT Retinoid X receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RXR.alpha.**, mRNA; suppression of retinoic acid receptor .beta. in
human non-small-cell **lung cancer in vivo**)

IT Retinoid X receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RXR.beta.**, mRNA; suppression of retinoic acid receptor .beta. in human
non-small-cell **lung cancer in vivo**)

IT Retinoid X receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**RXR.gamma.**, mRNA; suppression of retinoic acid receptor .beta. in
human non-small-cell **lung cancer in vivo**)

IT **Lung, neoplasm**

(adenocarcinoma; suppression of retinoic acid receptor .beta. in human
non-small-cell **lung cancer in vivo**)

IT Retinoid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mRNA; suppression of retinoic acid receptor .beta. in human
non-small-cell **lung cancer in vivo**)

IT **Lung, neoplasm**

(non-small-cell carcinoma; suppression of retinoic acid receptor .beta.
in human non-small-cell **lung cancer in vivo**)

IT mRNA

RL: BOC (Biological occurrence); BSU (Biological study, unclassified);
BIOL (Biological study); OCCU (Occurrence)
(retinoid receptor; suppression of retinoic acid receptor .beta. in
human non-small-cell **lung cancer in vivo**)

IT **Lung, neoplasm**

(squamous cell carcinoma; suppression of retinoic acid receptor .beta.
in human non-small-cell **lung cancer in vivo**)

IT Cell nucleus

(suppression of retinoic acid receptor .beta. in human non-small-cell
lung cancer in vivo)

L18 ANSWER 12 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 126:328891 CA

TITLE: **Modulation of retinoic acid sensitivity in
lung cancer cells through dynamic balance of
orphan receptors nur77 and COUP-TF and their**

09/919,195

heterodimerization
AUTHOR(S): Wu, Qiao; Li, Yin; Liu, Ru; Agadir, Anissa; Lee,
Mi-Ock; Liu, Yi; Zhang, Xiao-kun
CORPORATE SOURCE: La Jolla Cancer Res. Cent., Burnham Inst., La Jolla,
CA, 92037, USA
SOURCE: EMBO Journal (1997), 16(7), 1656-1669
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The diverse function of retinoic acid (RA) is mediated by its nuclear receptors, the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). However, the RA response is often lost in cancer cells that express the receptors. Previously, it was demonstrated that the RA response is regulated by the COUP-TF orphan receptors. Here, the authors present evidence that nur77, another orphan receptor whose expression is highly induced by phorbol esters and growth factors, is involved in modulation of the RA response. Expression of nur77 enhances ligand-independent transactivation of RA response elements (RAREs) and desensitizes their RA responsiveness. Conversely, expression of COUP-TF sensitizes RA responsiveness of RAREs by repressing their basal transactivation activity. Unlike the effect of COUP-TFs, the function of nur77 does not require direct binding of nur77 to the RAREs, but is through interaction between nur77 and COUP-TFs. The interaction occurs in soln. and results in inhibition of COUP-TF RARE binding and transcriptional activity. Unlike other nuclear receptors, a large portion of the carboxy-terminal end of nur77 is not required for its interaction with COUP-TF. In human lung cancer cell lines, COUP-TF is highly expressed in RA-sensitive cell lines while nur77 expression is assocd. with RA resistance. Stable expression of COUP-TF in nur77-pos., RA-resistant lung cancer cells enhances the inducibility of RAR.beta. gene expression and growth inhibition by RA. These observations demonstrate that a dynamic equil. between orphan receptors nur77 and COUP-TF, through their heterodimerization that regulates COUP-TF RARE binding, is crit. for RA responsiveness of human lung cancer cells.

TI Modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and their heterodimerization

SO EMBO Journal (1997), 16(7), 1656-1669
CODEN: EMJODG; ISSN: 0261-4189

AB The diverse function of retinoic acid (RA) is mediated by its nuclear receptors, the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). However, the RA response is often lost in cancer cells that express the receptors. Previously, it was demonstrated that the RA response is regulated by the COUP-TF orphan receptors. Here, the authors present evidence that nur77, another orphan receptor whose expression is highly induced by phorbol esters and growth factors, is involved in modulation of the RA response. Expression of nur77 enhances ligand-independent transactivation of RA response elements (RAREs) and desensitizes their RA responsiveness. Conversely, expression of COUP-TF sensitizes RA responsiveness of RAREs by repressing their basal transactivation activity. Unlike the effect of COUP-TFs, the function of nur77 does not require direct binding of nur77 to the RAREs, but is through interaction between nur77 and COUP-TFs. The interaction occurs in soln. and results in inhibition of COUP-TF RARE binding and transcriptional activity. Unlike other nuclear receptors, a large portion of the carboxy-terminal end of nur77 is not required for its interaction with COUP-TF. In human lung cancer cell lines, COUP-TF is highly expressed in RA-sensitive cell lines while nur77 expression is

- assocd. with RA resistance. Stable expression of COUP-TF in nur77-pos., RA-resistant lung cancer cells enhances the inducibility of RAR.beta. gene expression and growth inhibition by RA. These observations demonstrate that a dynamic equil. between orphan receptors nur77 and COUP-TF, through their heterodimerization that regulates COUP-TF RARE binding, is crit. for RA responsiveness of human lung cancer cells.
- ST nur77 COUPTF retinoate sensitivity lung cancer;
heterodimerization nur77 COUPTF retinoate sensitivity cancer
- IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(COUP-TF; modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAR-.beta.; modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RARE (retinoic acid-responsive element); modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Steroid receptors
Steroid receptors
Thyroid hormone receptors
Thyroid hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TR (thyroid/steroid hormone receptor); modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Transcriptional regulation
(activation; modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Gene
(expression; modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Molecular association
(heterodimerization; modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT Lung, neoplasm
(modulation of retinoic acid sensitivity in lung cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)
- IT 302-79-4, Retinoic acid

09/919,195

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(**modulation** of retinoic acid sensitivity in **lung**

cancer cells through dynamic balance of orphan receptors nur77 and COUP-TF and heterodimerization in relation to RARE genetic elements)

L18 ANSWER 13 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 126:207828 CA

TITLE: Retinoic acid receptor .epsilon. of human and expression of a cDNA encoding it and their therapeutic uses

INVENTOR(S): Cao, Liang; Ni, Jian; Fleischmann, Robert D.

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA

SOURCE: S. African, 49 pp.

CODEN: SFXAB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
	ZA 9404937	A	19950108	ZA 1994-4937	19940707 <--
PRIORITY APPLN. INFO.:				ZA 1994-4937	19940707
AB	A novel member of the human retinoic acid receptor family, RAR .epsilon., is identified and characterized and a cDNA encoding it is cloned and expressed. The receptor or the cDNA are of use in the diagnosis and treatment of diseases assocd. with abnormal levels of the receptor or of retinoic acid (no data) or in the identification of modulators of receptor activity. The mRNA for the receptor is abundant in testis, placenta, spleen, thymus and lung .				
PI	ZA 9404937 A		19950108		
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	ZA 9404937	A	19950108	ZA 1994-4937	19940707 <--
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IT	Lung Placenta Spleen Testis Thymus gland (retinoic acid receptor .epsilon. mRNA in; retinoic acid receptor .epsilon. of human and expression of cDNA encoding it and their therapeutic uses)				
IT	Retinoic acid receptors RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses) (.epsilon., (RAR .epsilon.)); retinoic acid receptor .epsilon. of human and expression of cDNA encoding it and their therapeutic uses)				

L18 ANSWER 14 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 123:246782 CA

TITLE: TGF-.beta. **modulates** the expression of retinoic acid-induced **RAR-.beta.** in primary cultures of embryonic palate cells

AUTHOR(S): Nugent, Paul; Potchinsky, Merle; Lafferty, Cynthia; Greene, Robert M.

CORPORATE SOURCE: Dep. Pathology, Anatomy Cell Biol., Jefferson Med. Coll., Philadelphia, PA, 19107, USA

SOURCE: Experimental Cell Research (1995), 220(2), 495-500
CODEN: ECREAL; ISSN: 0014-4827

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have previously shown that both transforming growth factor-.beta. (TGF-.beta.) and retinoic acid (RA) regulate the expression of cellular retinoic acid binding proteins (CRABP) I and II and TGF-.beta.3 mRNAs in primary cultures of murine embryonic palate mesenchymal (MEPM) cells. The authors now describe addnl. cross-talk between the RA and TGF-.beta. signal transduction pathways-the ability of TGF-.beta., including the endogenous form(s), to **modulate** the expression of the nuclear retinoic acid receptor-.beta. (**RAR-.beta.**). Northern blot hybridization revealed that RA induced the expression of **RAR-.beta.** mRNA, there being little or no detectable expression in untreated MEPM cells. Induction by 3.3 .mu.M RA was abrogated by simultaneous treatment with TGF-.beta.1 (5 ng/mL). TGF-.beta.1 alone had no effect on **RAR-.beta.** mRNA expression. Detn. of **RAR-.beta.** mRNA half-life by treatment with actinomycin D indicated that TGF-.beta.1 did not alter the stability of **RAR-.beta.** mRNA. Conditioned medium (CM) from MEPM cells contained little active TGF-.beta. protein; heat treatment of the CM dramatically increased the amt. of active TGF-.beta. as assessed by the mink lung epithelial cell bioassay. Furthermore, heat- or acid-activated CM also inhibited CRABP-I and RA-induced **RAR-.beta.** expression. The effect of heat-activated conditioned medium could be abrogated with panspecific neutralizing antibodies to TGF-.beta., confirming that endogenous TGF-.beta. is the biol. active factor in heat-activated CM. These results provide evidence for complex interactions between TGF-.beta. and RA in the regulation of gene expression of embryonic palatal cells and suggest a role for endogenous TGF-.beta. in the regulation of expression of genes encoding elements of the RA signal transduction pathway.

TI TGF-.beta. **modulates** the expression of retinoic acid-induced **RAR-.beta.** in primary cultures of embryonic palate cells

SO Experimental Cell Research (1995), 220(2), 495-500
CODEN: ECREAL; ISSN: 0014-4827

AB The authors have previously shown that both transforming growth factor-.beta. (TGF-.beta.) and retinoic acid (RA) regulate the expression of cellular retinoic acid binding proteins (CRABP) I and II and TGF-.beta.3 mRNAs in primary cultures of murine embryonic palate mesenchymal (MEPM) cells. The authors now describe addnl. cross-talk between the RA and TGF-.beta. signal transduction pathways-the ability of TGF-.beta., including the endogenous form(s), to **modulate** the expression of the nuclear retinoic acid receptor-.beta. (**RAR-.beta.**). Northern blot hybridization revealed that RA induced the expression of **RAR-.beta.** mRNA, there being little or no detectable expression in untreated MEPM cells. Induction by 3.3 .mu.M RA was abrogated by simultaneous treatment with TGF-.beta.1 (5 ng/mL). TGF-.beta.1 alone had no effect on **RAR-.beta.** mRNA expression. Detn. of **RAR-.beta.** mRNA half-life by treatment with actinomycin D indicated that TGF-.beta.1 did not alter the stability of **RAR-.beta.** mRNA. Conditioned medium (CM) from MEPM cells contained little

active TGF- β protein; heat treatment of the CM dramatically increased the amt. of active TGF- β as assessed by the mink lung epithelial cell bioassay. Furthermore, heat- or acid-activated CM also inhibited CRABP-I and RA-induced RAR- β expression. The effect of heat-activated conditioned medium could be abrogated with panspecific neutralizing antibodies to TGF- β , confirming that endogenous TGF- β is the biol. active factor in heat-activated CM. These results provide evidence for complex interactions between TGF- β and RA in the regulation of gene expression of embryonic palatal cells and suggest a role for endogenous TGF- β in the regulation of expression of genes encoding elements of the RA signal transduction pathway.

IT Signal transduction, biological
Teratogens

(TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

IT Ribonucleic acids, messenger

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(for retinoic acid receptor- β ; TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(CRABP-I (cellular retinoic acid-binding protein I), TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

IT Receptors

Retinoid receptors

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(RAR- β (retinoic acid receptor β), TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

IT Animal growth regulators

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(β -transforming growth factors, TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

IT 302-79-4, Retinoic acid

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(TGF- β modulates expression of retinoic acid-induced RAR- β in primary cultures of embryonic palate cells)

L18 ANSWER 15 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 122:154423 CA

TITLE: Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors

AUTHOR(S): Song, Ching; Kokontis, John M.; Hiipakka, Richard A.; Liao, Shutsung

CORPORATE SOURCE: The Ben May Inst. Dep. Biochem. Mol. Biol., Univ. Chicago, Chicago, IL, 60637, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1994), 91(23), 10809-13

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

- AB The cDNA for a member of the nuclear receptor family was cloned and named ubiquitous receptor (UR), since UR protein and mRNA are detected in many cell types. Rat UR/human retinoid X receptor .alpha. (hRXR.alpha.) heterodimers bound preferentially to double-stranded oligonucleotide direct repeats having the consensus half-site sequence AGGTCA and 4-nt spacing (DR-4). Coexpression of UR in COS-1 cells inhibited the stimulation of chloramphenicol acetyltransferase (CAT) reporter gene expression by hRXR.alpha. and human retinoic acid receptor .alpha. in the presence of all-trans-retinoic acid when DR-4 (but not DR-5) was present upstream of the promoter of a CAT reporter gene (DR-4-CAT). UR expression also inhibited the activation of a DR-4-CAT reporter gene by hRXR.alpha. and 9-cis-retinoic acid or by thyroid hormone receptor .beta. in the presence of thyroid hormone. However, in the absence of 9-cis-retinoic acid, UR in combination with hRXR.alpha. stimulated DR-4-CAT expression. Coexpression of thyroid hormone receptor markedly reduced this stimulation in the absence of thyroid hormone. UR may play an important role in normal growth and differentiation by **modulating** gene activation in retinoic acid and thyroid hormone signaling pathways.
- TI Ubiquitous receptor: a receptor that **modulates** gene activation by retinoic acid and thyroid hormone receptors
- SO Proceedings of the National Academy of Sciences of the United States of America (1994), 91(23), 10809-13
CODEN: PNASA6; ISSN: 0027-8424
- AB The cDNA for a member of the nuclear receptor family was cloned and named ubiquitous receptor (UR), since UR protein and mRNA are detected in many cell types. Rat UR/human retinoid X receptor .alpha. (hRXR.alpha.) heterodimers bound preferentially to double-stranded oligonucleotide direct repeats having the consensus half-site sequence AGGTCA and 4-nt spacing (DR-4). Coexpression of UR in COS-1 cells inhibited the stimulation of chloramphenicol acetyltransferase (CAT) reporter gene expression by hRXR.alpha. and human retinoic acid receptor .alpha. in the presence of all-trans-retinoic acid when DR-4 (but not DR-5) was present upstream of the promoter of a CAT reporter gene (DR-4-CAT). UR expression also inhibited the activation of a DR-4-CAT reporter gene by hRXR.alpha. and 9-cis-retinoic acid or by thyroid hormone receptor .beta. in the presence of thyroid hormone. However, in the absence of 9-cis-retinoic acid, UR in combination with hRXR.alpha. stimulated DR-4-CAT expression. Coexpression of thyroid hormone receptor markedly reduced this stimulation in the absence of thyroid hormone. UR may play an important role in normal growth and differentiation by **modulating** gene activation in retinoic acid and thyroid hormone signaling pathways.
- IT Adrenal gland
Brain
Heart
Kidney
Liver
Lung
Ovary
Prostate gland
Spleen
Testis
Uterus
Vagina
(mRNA expression; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT Fibroblast
(skin; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT Protein sequences

- Rat
Signal transduction, biological
(ubiquitous receptor **modulating** human and mouse gene
activation by retinoic acid and thyroid hormone receptors)
- IT Ribonucleic acids, messenger
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);
BIOL (Biological study); OCCU (Occurrence)
(ubiquitous receptor **modulating** human and mouse gene
activation by retinoic acid and thyroid hormone receptors)
- IT Thyroid hormones
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(ubiquitous receptor **modulating** human and mouse gene
activation by retinoic acid and thyroid hormone receptors)
- IT Ribonucleic acid formation factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study); PROC (Process)
(ubiquitous receptor; ubiquitous receptor **modulating** human
and mouse gene activation by retinoic acid and thyroid hormone
receptors)
- IT Animal cell line
(3T3, ubiquitous receptor **modulating** human and mouse gene
activation by retinoic acid and thyroid hormone receptors)
- IT Animal cell line
(BJAB, human B-cell; ubiquitous receptor **modulating** human and
mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT Animal cell line
(LNCaP, prostate carcinoma; ubiquitous receptor **modulating**
human and mouse gene activation by retinoic acid and thyroid hormone
receptors)
- IT Animal cell line
(PC-3, prostate carcinoma; ubiquitous receptor **modulating**
human and mouse gene activation by retinoic acid and thyroid hormone
receptors)
- IT Receptors
Retinoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(RAR-.alpha. (retinoic acid receptor .alpha.), ubiquitous
receptor **modulating** human and mouse gene activation by
retinoic acid and thyroid hormone receptors)
- IT Animal cell line
(RPMI-1788, ubiquitous receptor **modulating** human and mouse
gene activation by retinoic acid and thyroid hormone receptors)
- IT Retinoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(RXR.alpha. (retinoic acid receptor X .alpha.), ubiquitous receptor
modulating human and mouse gene activation by retinoic acid and
thyroid hormone receptors)
- IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(RXR.alpha. (retinoid X receptor .alpha.), ubiquitous receptor
modulating human and mouse gene activation by retinoic acid and
thyroid hormone receptors)
- IT Animal cell line
(WEHI-231, mouse immature B-cell; ubiquitous receptor
modulating human and mouse gene activation by retinoic acid and

- thyroid hormone receptors)
- IT Deoxyribonucleic acid sequences
(complementary, ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thyroid hormone .beta., ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT Thyroid hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta., ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT 159845-69-9 159845-70-2 159845-71-3 159845-72-4 159845-73-5
159845-74-6 159845-75-7
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA binding site; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT 159966-44-6, Ribonucleic acid factor (rat clone R6.2) 159966-45-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT 159199-63-0 161050-10-8
RL: PRP (Properties)
(nucleotide sequence; ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)
- IT 302-79-4, all-trans-Retinoic acid 5300-03-8, 9-cis-Retinoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ubiquitous receptor **modulating** human and mouse gene activation by retinoic acid and thyroid hormone receptors)

L18 ANSWER 16 OF 16 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 112:230122 CA
TITLE: Indirect effects of histamine on pulmonary rapidly adapting receptors in cats
AUTHOR(S): Yu, Jun; Roberts, Andrew M.
CORPORATE SOURCE: Sch. Med., Univ. Louisville, Louisville, KY, 40292, USA
SOURCE: Respiration Physiology (1990), 79(2), 101-10
CODEN: RSPYAK; ISSN: 0034-5687
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relative importance of lung mech. changes during histamine-induced activation of pulmonary rapidly adapting receptors (RARs) was investigated. In anesthetized, open-chest, artificially ventilated cats, the authors recorded RAR activity and injected histamine (25-50 .mu.g/kg) into the right atrium. Histamine initially increased RAR activity from 1.1 to 3.6 imp/s at 15.6 s when dynamic lung compliance (CDYN) was decreased by 29.1%. The firing pattern of RARs changed from a relatively irregular pattern to a pronounced respiratory **modulation**. RAR activity reached its peak (5.6 imp/s) at 36.3 s. The firing pattern further

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changed to a cardiac **modulation**, and the activity closely correlated with cardiac output. On comparing the initial response of RARs to histamine with the response to mech. decreasing CDYN, the activities were similar when CDYN was decreased by the same amt. In cats, the initial increase of RAR activity in response to histamine is apparently related to **lung** mech. changes, but the later increase is related to cardiovascular functions.

SO Respiration Physiology (1990), 79(2), 101-10

CODEN: RSPYAK; ISSN: 0034-5687

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ST histamine **lung** rapidly adapting receptor; cardiovascular system
lung histamine; receptor **lung** compliance histamine

IT Blood pressure
(histamine effect on, **lung** rapidly adapting receptors in relation to)

IT **Lung**, composition
(rapidly adapting receptors of, histamine effect on)

IT 51-45-6, Histamine, biological studies

RL: BIOL (Biological study)

(**lung** rapidly adapting receptors response to)

=> FIL STNGUIDE

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

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87.60

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TOTAL

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SESSION

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

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